McNeil
Consumer & Specialty Pharmaceuticals

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DOCKET NO. 2005P-0048/CP1: SUPPLEMENT TO CITIZEN PETITION

On January 31, 2005, McNeil Consumer & Specialty Pharmaceuticals, a Division of McNeil-PPC, Inc. (McNeil), Fort Washington, PA, submitted a Citizen Petition (Petition) under section 505 of the Federal Food, Drug, and Cosmetic Act, and 21 C.F.R. § 10.30. The Petition[1] requested that the Commissioner of Food and Drugs approve a change in the professional labeling for aspirin dosing under 21 C.F.R. 343.80, in order to specify the more favorable benefit/risk profile of aspirin doses of 75–150 mg/day for secondary cardiovascular prevention, and 50–150 mg/day for secondary cerebrovascular prevention.

On May 4, 2005, Bayer HealthCare Consumer Care Division (Bayer), submitted to Docket No. 2005P-0048 comments on McNeil's Petition, which included a recommendation that it would be inappropriate to modify the dosage range for aspirin for the currently approved professional indications. McNeil addresses Bayer's comments and is submitting a Supplement under 21 C.F.R. § 10.30(g) to its above referenced Petition.

I. BACKGROUND SUMMARY: PUBLIC HEALTH NEED AND SCIENTIFIC EVIDENCE IN MCNEIL'S PETITION

Preventing heart disease and stroke is one of our nation's major healthcare objectives. More than 70 million Americans have some form of cardiovascular disease, including coronary heart disease, stroke and other conditions. National strategies include overall health promotion as well as primary and secondary prevention.[2,3] Secondary prevention strategies include ensuring the use of aspirin therapy in populations with established

[1] McNeil Citizen Petition of 01/31/2005 FDA docket 2005P-0048/CP1.
[2] CDC. National Center for Chronic Disease Prevention & Health Promotion, Cardiovascular Health. Website: www.cdc.gov/cvh. Accessed August 2, 2005.
[3] CDC. Healthy People 2010, Heart Disease and Stroke Objectives. Website: www.cdc.gov/cvh/hp2010/objectives.htm. Accessed August 2, 2005.

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cardio- and cerebrovascular disease.[4] Scientific data in McNeil's Petition support that the upper range of the currently recommended aspirin daily dose (i.e., 151–325 mg) for secondary prevention, has an increased risk of major bleeding events, in particular GI bleeding, without providing superior benefit when compared to aspirin daily doses of ≤150 mg.

McNeil considers that all the material and methods used by the FDA to reach the scientific and regulatory conclusions enunciated in the Federal Register notices of 1988, 1996, and 1998 (63 FR § 56802), as well as the PRAVIGARD™ PAC (NDA 21-387) approval of new labeling for buffered aspirin for vascular indications, provide the critical background information for consideration of McNeil's Petition request to change the professional labeling for aspirin dosing under 21 C.F.R. 343.80.

McNeil's Petition requested that the professional labeling for aspirin specify the more favorable safety profile of aspirin doses of 75–150 mg daily for secondary cardiovascular prevention, and 50–150 mg daily for secondary cerebrovascular prevention to provide effective treatment and minimize major bleeding events, particularly GI bleeding. Since aspirin daily doses >150 mg do not provide superior efficacy when compared with aspirin daily doses of ≤150 mg, recommending higher (>150 mg daily) aspirin doses merely exposes patients to a higher risk of major bleeding events, particularly GI bleeding.

McNeil's Petition is supportive of FDA's Risk Minimization initiatives which focus on the appropriate drug at the appropriate dose in order to minimize the risk to patients while ensuring beneficial effects. As it relates to aspirin therapy for secondary cardio- and cerebrovascular prevention, McNeil's Petition provides a comprehensive evidence-based risk assessment in relation to the benefits of low-dose (≤150 mg/day) aspirin.

Overall, nothing in Bayer's comments negates the significance of the scientific evidence supporting McNeil's Petition. Moreover, Bayer's comments direct attention away from the important public health need, as well as the scientific evidence supporting the need for professional aspirin labeling that provides a more favorable benefit/risk profile with low-dose (≤150 mg/day) aspirin therapy for secondary cardio- and cerebrovascular prevention.

[4] CDC. Promising Practices in Chronic Disease prevention and Control: A Public Health Framework for Action. Achieving a Heart-Healthy and Stroke-Free Nation. Website: www.cdc.gov/nccdphp/promising_practices/heart/opportunities.htm. Accessed August 2, 2005.

II. MCNEIL COMMENTS ON BAYER'S RESPONSE

Bayer puts forward objections to the McNeil Petition in the following areas:

A. Clinical Trial Safety and Efficacy of Low-Dose (≤150 mg/day) Aspirin: Overall, Bayer asserts that data do not show evidence of an increased GI risk within the range of aspirin doses of 50–325 mg/day for secondary cardio- and cerebrovascular prevention. In addition, Bayer states, "there are no meaningful differences in effectiveness across the aspirin 75–325 mg per day dose range."

B. The Phenomenon of "Aspirin Resistance": Bayer claims that some individuals exhibit "aspirin resistance" and that they may achieve improved clinical outcomes with a higher dose of aspirin.

C. Patient Subpopulations: Bayer claims that a higher dose of aspirin may achieve improved effectiveness in patients with stroke, with diabetes, those who smoke, and those who have elevated body weight.

D. Professional Guidelines: Bayer states that professional guidelines support a higher dose of aspirin therapy for secondary cardio- and cerebrovascular prevention.

These issues are addressed, sequentially, as "A", "B", "C", and "D", below.

A. CLINICAL TRIAL DATA DEMONSTRATE LOW-DOSE ASPIRIN (≤150 MG/DAY) HAS LOWER RISK OF MAJOR BLEEDING THAN HIGH-DOSE (>150 MG/DAY) ASPIRIN AND HAS COMPARABLE EFFICACY

1. Lower Bleeding Risk With Low-Dose (≤150 mg/day) Aspirin

Bayer asserts that sufficient data are not available to show an increased GI risk within the range of aspirin doses of 50–325 mg/day. Bayer cites three references as support: two of Bayer's citations are uninformative because they do not provide any comparisons between different aspirin doses within the range of 50–325 mg/day. The first is The U.S. Preventive Services Task Force (Hayden et al., 2000) which provides a clinical guideline on aspirin for primary prevention of cardiovascular events.[5] Within this citation, a meta-analysis of efficacy and safety data is provided from five primary prevention trials of aspirin. Based on these data, the Task Force reported an increase in major extracranial bleeding with aspirin use (odds ratio (OR) 1.7); no aspirin dose-response safety data were reported.

[5] Hayden M, Pignone M, Phillips C, et al. Aspirin for the primary prevention of cardiovascular events: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2002;136:161-172.

The second citation is that of Derry and Loke (2000), a meta-analysis of 24 randomized, placebo-controlled trials that was conducted to determine the incidence of GI hemorrhage associated with long-term aspirin therapy in stroke patients and in patients taking aspirin for primary prevention of cardiovascular disease.[6] Aspirin doses ranged from 50 to 1500 mg/day and were taken for a minimum of one year. Combining all 24 trials, GI hemorrhage occurred in 2.47% of patients taking aspirin vs. 1.42% of patients taking placebo. While not statistically significant (p=0.3), a meta-regression analysis of the 24 trials showed a relative reduction in the incidence of GI hemorrhage of 1.5% per 100 mg reduction of dose.

When eight trials of patients using aspirin doses of 50–162.5 mg/day were analyzed separately, aspirin was associated with a significant increase in GI hemorrhage rate compared to that of placebo (2.30% and 1.45% for aspirin and placebo, respectively [OR=1.59, p<0.0001]). Safety comparisons between different aspirin doses within the range of 50–325 mg/day were not performed and, as such, this study is uninformative in this regard.

In sum, the results of the meta-analysis by Derry and Loke (2000) support the well-established conclusion that aspirin doses as low as 50 mg/day increased the risk of GI hemorrhage when compared to placebo.[6] This study is uninformative in regards to assessing GI risk between aspirin doses of interest.

Bayer also cites The Antithrombotic Trialists Collaboration (ATC) (2002) meta-analysis, which included a total of 212,000 patients from 287 randomized trials who were at increased risk of occlusive events.[7] This was designed primarily as an efficacy analysis to determine the effects of aspirin and other antiplatelet therapies among patients at high annual risk (over 3% a year) of vascular events based on evidence of pre-existing disease (previous occlusive event or predisposing condition). Comparisons of different aspirin daily dose ranges (i.e., <75 mg, 75–150 mg, 160–325 mg and 500–1500 mg daily) from this meta-analysis comprise convincing efficacy data that low daily doses of aspirin (75–150 mg/day) are at least as effective as higher daily doses (≥160 mg/day) in reducing the incidence of nonfatal MI, nonfatal stroke, and vascular death.

It was reported in ATC (2002) that the proportional increase in the risk of a major extracranial bleed was similar with all daily aspirin doses ≤325 mg versus control (i.e.,

[6] Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long-term use of aspirin: meta-analysis. *BMJ.* 2000;321:1183-1187.
[7] Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *BMJ.* 2002;324:71-86.

antiplatelet drugs). However, the control group was not explicitly stated as whether it was aspirin and/or other antiplatelet therapies. Thus, this comparison may not be appropriate to address the assessment of GI risk within the aspirin dose range of interest. In addition, since the primary analysis was of efficacy, the study was not designed to detect differences in major extracranial bleeds between different aspirin doses.

Of the 60 studies with at least one aspirin-only arm, 19 reported "data unavailable" for major extracranial bleeds (i.e., fatal or nonfatal). However, two trials in ATC directly compared aspirin dose groups of <75 mg to 75–325 mg daily. The combined analysis of these two trials found a lower rate (i.e., 1.8% [28 of 1555 subjects]) of major extracranial bleeding in the <75 mg aspirin dose group compared to a higher rate (i.e., 2.5% [39 of 1575 subjects]) in the aspirin dose group of 75–325, which was reported as statistically not significant. The 28% reduction in the incidence rate (i.e., reduction from 2.5% to 1.8%) of major extracranial bleeding is a substantially meaningful reduction.

In sum, Bayer inappropriately interprets the findings of Hayden et al. (2002) and Derry and Loke (2000) as relates to GI risk within the range of aspirin doses of 50–325 mg/day, since neither reported comparing different aspirin doses of interest. In ATC (2002), the data from the two trials comparing aspirin doses within the range of interest showed a 28% reduction in the incidence of major extracranial bleeding with the <75 mg aspirin dose group compared to the higher dose group. This ATC finding is consistent with the body of scientific evidence provided in McNeil's Petition[1], which indicates that, within the aspirin dose range of 50–325 mg/day for secondary prevention, more major bleeding events occur with high-dose (>150 mg daily) aspirin than with low-dose (≤150 mg daily) aspirin.

2. Randomized Clinical Trials – DUTCH TIA, UK-TIA and ACE

Bayer introduces and then inappropriately criticizes randomized clinical trials—Dutch TIA, UK-TIA, and ACE—simply because at least one aspirin dose studied in each trial fell outside of the current professional labeling for aspirin dosing under 21 CFR § 343.80. In fact, both the Dutch TIA and UK-TIA trials were among the clinical trials reviewed by FDA in determining the adverse reactions section of professional aspirin labeling, which states, "Many adverse reactions due to aspirin ingestion are dose-related." Despite their criticism, Bayer correctly notes that the results of these trials comparing different aspirin doses support that a lower dose of aspirin is as effective as a higher dose of aspirin.

The Dutch TIA trial[8] studied 3131 patients who had a TIA or minor ischemic stroke in the preceding three months. The study compared the efficacy of aspirin 30 mg daily to that of aspirin 283 mg daily. The primary endpoint was the combined event of death from all vascular causes, nonfatal stroke, or nonfatal MI, which ever occurred first. The aspirin 30 mg dose was reported as effective as the aspirin 283 mg dose (the adjusted hazard ratio for the primary endpoint 0.91 [95% CI 0.76-1.09]). There was a nonsignificantly lower rate of major bleeding events and a significantly lower rate of minor bleeding events in the patients receiving 30 mg per day of aspirin. The authors concluded that, "30 mg of aspirin is no less effective in the prevention of vascular events than a 283 mg dose in patients with a transient ischemic attack or minor stroke, and has fewer adverse effects."

The UK-TIA Study Group[9] evaluated 2448 patients who had a recent TIA or minor ischemic stroke and compared the efficacy of aspirin doses at 1200 mg and 300 mg daily. The primary composite endpoint was nonfatal major stroke, nonfatal MI, vascular death or nonvascular death. The investigators reported that, "There were...no significant differences between the two dose levels of aspirin." They also reported that, "Analysis of the two different daily doses studied showed highly significantly greater gastrotoxicity with the high dose [aspirin] regimen but no clear differences in therapeutic effect."

The ACE trial (Taylor et al., 1999) was a multicenter, randomized, double-blind, controlled trial of aspirin at doses of 81, 325, 650, and 1300 mg/day in adult patients who were scheduled to undergo carotid endarterectomy for arteriosclerotic disease.[10] A total of 2804 patients were enrolled. Patients were treated with aspirin prior to and for three months following surgery. The primary objective of the study was to evaluate differences in the occurrence of perioperative complications (stroke, MI, and death) at 30 days and three months after surgery among patients receiving four different doses of aspirin. The primary efficacy analysis in the ACE trial compared the high-dose group (650 and 1300 mg/day) to the low-dose group (81 and 325 mg/day). Comparisons between the individual 81 and 325 mg/day doses and the 650 and 1300 mg/day doses were performed as secondary analyses. The composite endpoints were all strokes, MIs, and deaths; all strokes and deaths; and ipsilateral strokes and deaths. The authors

[8] The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor stroke. *NEJM.* 1991;325:1261-1266.
[9] UK-TIA Study Group. United Kingdom Transient Ischaemic Attack (UK-TIA) aspirin trial: interim results. *BMJ.* 1988;296:316-320.
[10] Taylor D, Barnet H, Haynes R, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarectomy: a randomized controlled trial. *Lancet.* 1999;353:2179-2184.

reported that, "There were no significant differences between the 81 mg and 325 mg [aspirin] groups...in any of the [efficacy] analyses."

In the ACE trial, safety endpoints were the incidence of hemorrhagic stroke, wound haematoma, and gastric or intestinal disorders. Bayer states that, "GI bleeding complications were identical in the 325 mg vs. 81 mg [aspirin] groups (8 events vs. 8 events)." Since the primary analysis was of efficacy, the study was not designed to detect differences in safety endpoints between different aspirin doses. No statistical comparisons between the individual 81 and 325 mg/day aspirin doses (i.e., within the dose range of interest) were reported. As such, no inference can be made based on these safety data.

In sum, scientific evidence from randomized clinical trials—the Dutch TIA, UK-TIA, and ACE trial—demonstrates that lower doses of aspirin are as effective as higher doses of preventive aspirin for vascular indications. These findings are consistent with the body of scientific evidence in McNeil's Petition supporting that low-dose (≤150 mg daily) aspirin has been demonstrated to be as effective as high-dose (>150 mg daily) aspirin for the secondary prevention of serious vascular events (nonfatal myocardial infarction, nonfatal stroke, or vascular death).

3. *Meta-Analyses of Randomized Clinical Trials – ATC, Serebruany, and Derry and Loke*

In their comments, Bayer misstates the principal conclusion from the Antithrombotic Trialists Collaboration (ATC) (2002), a meta-analysis including a total of 212,000 patients who were at increased risk of occlusive events from 287 randomized trials.[7]

As background, ATC's primary objective of the efficacy analysis was to determine the effects of aspirin and other antiplatelet therapies among patients at high annual risk (over 3% a year) of vascular events based on evidence of pre-existing disease (previous occlusive event or predisposing condition). Comparisons of different aspirin daily dose ranges (i.e., <75 mg, 75–150 mg, 160–325 mg and 500–1500 mg daily) from this meta-analysis comprise some of the most convincing efficacy data that low daily doses of aspirin (75–150 mg/day) are at least as effective as higher daily doses (≥160 mg/day) in reducing the incidence of nonfatal MI, nonfatal stroke, and vascular death. Bayer misstates the conclusion as, "there are no meaningful differences in effectiveness across the aspirin 75–325 mg per day dose range." In fact, the authors of the ATC meta-analysis reported, "Daily aspirin doses of 75–150 mg seem to be as effective as higher doses for long term treatments [i.e., the prevention of vascular events]."

Bayer criticizes a meta-analysis by Serebruany et al. (2004)[11] by stating that the "results are inconsistent and represent the confounding that is present in such an analysis." Bayer's suggestion appears to be based on results showing that 325 mg was the aspirin dose above which major bleeding events increased and 100 mg was the dose above which minor bleeding events increased.

As provided in McNeil's Petition, the Serebruany et al. (2004) meta-analysis comprised 50 randomized clinical trials of 338,191 patients to assess the risk of hemorrhage associated with various antiplatelet agents, including aspirin.[11] Patients were analyzed based on their exposure to aspirin doses of <100 mg/day, 100–325 mg/day, or >325 mg/day. Bleeding complications analyzed included major and minor bleeding events, hemorrhagic stroke, GI bleeding events, and total bleeding events. Table 1 provides results from Serebruany et al. (2004) for weighted average bleeding rates for major, minor, GI and total bleeding by aspirin daily dose.

Table 1. Weighted Average for Major, Minor, GI and Total Bleeding Rates by Aspirin Daily Dose (Serebruany et al., 2004)[11]

Aspirin Dose (mg/day)	Number of Trials Reported	Number of Patients	Bleeding Rate (%)	95% CI
Major Bleeding				
<100 mg	5	13,337	1.7	1.4 to 1.9
100-325 mg	11	43,489	1.7	1.5 to 1.8
>325 mg	2	1409	2.5	1.7 to 3.3
Minor Bleeding				
<100 mg	3	11,963	1.8	1.5 to 2.0
100-325 mg	5	13,588	6.5	6.1 to 6.9
>325 mg[a]	0	0	Not applicable	Not applicable
GI Bleeding				
<100 mg	5	13,337	1.1	0.9 to 1.3
100-325 mg	7	30,413	2.4	2.2 to 2.6
>325 mg	3	2224	2.5	1.8 to 3.1
Total Bleeding				
<100 mg	4	12,639	3.6	3.3 to 3.9
100-325 mg	6	22,745	9.1	8.7 to 9.4
>325 mg	1	1540	9.9	8.4 to 11.4

a: No trials reported minor bleeding events for this dose range.

Overall, the Serebruany et al. (2004) results across all of the weighted average bleeding rates by all of the aspirin doses support a higher incidence of clinically important

[11] Serebruany VL, Malinin AL, Eissert RM, et al. Risk of bleeding complications with antiplatelet agents: Meta-analysis of 338,191 patients enrolled in 50 randomized controlled trials. *Amer J Hematol.* 2004;75(1):40-47.

bleeding events (i.e., not minor bleeding events) with increasing daily aspirin doses. Also, results showed that the aspirin dose of <100 mg daily consistently had the lowest weighted average bleeding rates.

Bayer fails to note a more recent analysis by Serebruany et al. (2005)[12], which was designed to better understand the optimal dose of aspirin with respect to clinically important bleeding events. As provided in McNeil's Petition, Serebruany et al. (2005) analyzed different aspirin dose groups from those in their 2004 analysis.[12] The following aspirin dose groups were examined: low (<100 mg/day), moderate (100–200 mg/day), and high (>200 mg/day). Data for these three aspirin dose groups were available from 31 clinical trials with a total of 192,036 patients. These specific aspirin dose ranges are identical to those reported in the Adverse Reactions section (Table 3: CURE incidence of bleeding complications) from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) study as included in prescribing information of PLAVIX (clopidogrel bisulfate), November 2004.[13]

Table 2 provides results from Serebruany et al. (2005) for weighted average bleeding rates for major, GI and total bleeding by aspirin daily dose. The aspirin dose groups of <100 mg/day and 100–200 mg/day had the lowest major and GI bleeding rates. For total bleeding events, the aspirin daily dose of <100 mg/day showed the lowest rate.

Table 2. Weighted Average for Major, GI and Total Bleeding Rates by Aspirin Daily Dose (Serebruany et. al. 2005)[12]

Aspirin Dose (mg/day)	Number of Trials Reported	Number of Patients	Bleeding Rate (%)	95% CI
Major Bleeding				
<100 mg	8	17,202	1.56	1.2 to 1.8
100–200 mg	8	32,223	1.54	1.4 to 1.8
>200 mg	10	19,758	2.29	1.9 to 7.0
GI Bleeding				
<100 mg	8	17,779	0.97	0.7 to 1.3
100–200 mg	1	3,311	0.39	Not applicable
>200 mg	7	28,378	2.69	1.8 to 3.1
Total Bleeding				
<100 mg	7	17,462	3.72	3.1 to 3.7
100–200 mg	2	6,385	11.31	8.9 to 13.2
>200 mg	6	15,472	9.8	7.2 to 10.8

[12] Serebruany VL, Steinhubl SR, Berger PB, et al. The risk of bleeding after different doses of aspirin: A post-hoc analysis of 192,036 patients enrolled in 31 randomized controlled trials. *Am J Card.* 2005;95:1218-1222.
[13] PLAVIX (clopidogrel bisulfate) Prescribing Information, issued November 2004.

In contrast to Bayer's criticism of inconsistent results, the two Serebruany et al. (2004 and 2005) publications demonstrate that the lowest weighted average bleeding rates for major, GI, and total bleeding were consistently found with aspirin daily dose groups of <100 mg and 100–200 mg.

Bayer cites for a second time in their comments, a meta-analysis conducted by Derry and Loke (2000). Bayer states, "it can be concluded that there is no meaningful correlation between GI bleeding and dose." As provided in McNeil's Petition, Derry and Loke (2000) conducted a meta-analysis of 24 randomized, placebo-controlled trials to determine the incidence of GI hemorrhage associated with long-term aspirin therapy in stroke patients and in patients taking aspirin for primary prevention of cardiovascular disease. Aspirin doses ranged from 50 to 1500 mg/day and were taken for a minimum of one year. Combining all 24 trials, GI hemorrhage occurred in 2.47% of patients taking aspirin vs. 1.42% of patients taking placebo. While not statistically significant (p=0.3), a meta-regression analysis of the 24 trials showed a relative reduction in the incidence of GI hemorrhage of 1.5% per 100 mg reduction of dose.

When eight trials of patients using aspirin doses of 50–162.5 mg/day were analyzed separately, aspirin was associated with a significant increase in GI hemorrhage rate compared to that of placebo (2.30% and 1.45% for aspirin and placebo, respectively, [OR=1.59, p<0.0001]). Safety comparisons between different aspirin doses within the range of 50–325 mg/day were not performed and, as such, this study is uninformative in this regard.

In sum, the results of the meta-analysis by Derry and Loke (2000) support the well-established conclusion that aspirin doses, even as low as 50 mg/day, increase the risk of GI hemorrhage versus placebo. This study is uninformative in regards to assessing GI risk between aspirin doses of interest.

4. The Appropriateness, Applicability and Utility of Meta-Analyses

Bayer contends that indirect comparisons like the meta-analyses of ATC (2002) and Serebruany et al. (2004) are subject to significant confounding. Bayer offers no support for their allegation of confounding. Experts describe that, in order to minimize confounding and other forms of bias, it is generally accepted that certain key principles be followed when designing and conducting a meta-analysis[14]; both the ATC (2002)

[14] Berlin JA. The use of meta-analysis in pharmacoepidemiology. In: Strom BL, ed. *Pharmacoepidemiology.* 3rd ed. West Sussex, England, UK: John Wiley & Sons, Ltd; 2000:633–659.

investigators and Serebruany et al. (2004 and 2005) reported methods consistent with such principles. [7,11,12]

Bayer provides two opposing positions about the conclusiveness of meta-analysis. On the one hand, Bayer states that the ATC (2002) and Serebruany et al. (2004) meta-analyses are merely hypothesis generating and should not be used to influence the choice of treatments. On the other hand, Bayer refers to the data from the Derry and Loke (2000) meta-analysis as being conclusive. Experts have stated that meta-analyses are not merely hypothesis generating and have described their appropriateness and applicability and their utility in developing clinical recommendations. Although rigorously designed double-blind randomized trials offer the most valid scientific evidence, such trials are often limited by inadequate sample size that leaves them open to missing important differences between treatment groups. By quantitatively combining the results of several small studies, meta-analyses can create more precise, powerful, and convincing conclusions and increase confidence in the applicability of the results to widely diverse groups of patients. [14,15,16,17]

With regard to safety, adverse events associated with drugs are often so uncommon as to be difficult to study. Investigating these adverse events is an important application of meta-analysis. By combining results from many randomized studies, meta-analysis can address the problem of rare events and rectify the associated lack of adequate statistical power in a setting free of the confounding and bias of nonexperimental studies. Meta-analysis provides the benefit of vastly increased statistical power to investigate adverse events. [14]

5. Recent Randomized Clinical Trials: CURE and BRAVO

Bayer notes two recent randomized, double-blind, placebo-controlled clinical trials that were detailed in McNeil's Petition (Peters et al. (2003) CURE[18], and Topol et al. (2003) BRAVO[19]). Bayer points out potential confounding in both studies, and suggests that their results are hypothesis generating. Bayer ignores the significance of the low-dose aspirin safety findings from the CURE and BRAVO clinical trials.

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[15] Cook DJ, Guyatt GH, Laupacis A, Sackett DL, Goldberg RJ. Clinical recommendations using levels of evidence for antithrombotic agents. *Chest.* 1995;108:227–230.

[16] Guyatt GH, Sackett DL, Sinclair JC, et al., Users's guides to the medical literature - IX. A method for grading health care recommendations. *JAMA.* 1995;274:1800-1804.

[17] Berlin JA, Coldiz GA. The role of meta-analysis in the regulatory process for foods, drugs, and devices. *JAMA.* 1999;281(9)830-844.

[18] Peters RJD, Mehta SR, Fox KAA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in unstable angina to prevent recurrent events (CURE) study. *Circulation.* 2003;108(14):1682-1687.

[19] Topol EJ, Easton D, Harrington RA, et al. Randomized, double-blind, placebo-controlled, international trial on the oral IIb/IIIa antagonist lotrafiban in coronary and cerebrovascular disease. *Circulation.* 2003;108(4):399-406.

Bayer's critique of the CURE trial claims that aspirin doses were "arbitrarily" divided into three groups, that aspirin doses were only recorded or tracked at study entry, and that the data are subject to confounding by indication, co-morbidities and region.

As detailed in McNeil's Petition, Peters et al. (2003) conducted a post-hoc analysis of the CURE study, a randomized, double-blind, placebo-controlled study that was designed to evaluate the benefits and risks of adding clopidogrel to different doses of aspirin in patients with ACS. A total of 12,562 patients from 28 countries were enrolled in the study. The risk of major and minor bleeding at various aspirin doses was assessed. In the aspirin plus placebo group (i.e. aspirin-alone), the incidence of major bleeding increased significantly with increasing aspirin dose (1.9%, 2.8%, and 3.7% for aspirin doses of ≤100, 101–199, and ≥200 mg/day, respectively; p-value for trend, < 0.0001).[18] Findings of a significant increase in major bleeding events with increasing aspirin doses are also described in the Adverse Reactions section (Table 3: CURE incidence of bleeding complications) of the prescribing information for PLAVIX (clopidogrel bisulfate), November 2004.[13]

In the CURE study, the three aspirin dose groups were assigned based on physicians' prescribing habits in different geographical regions, not patient risk factors. The CURE study investigators state, "...the main determinant of the dose used in patients in CURE was the routine approach of centers and specific countries. This argues against the possibility that the selection of dose may be related to the risk profiles of patients, thus confounding the differences in efficacy or safety between dose groups...". As reported by these same investigators, a dose-response relationship between aspirin and bleeding complications was observed even after adjustments were made for region, gender, body mass index, smoking status, myocardial infarction history, diabetes, hypertension, history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), and Thrombolysis in Myocardial Infarction (TIMI) risk score. Based on this, it is unlikely that significant confounding occurred. Also, Bayer's statement that changes in the aspirin dose were not tracked throughout the study is false. As reported by the CURE investigators, aspirin dose was recorded at study entry and at months 1, 3, 6, 9, and 12.

In regards to the BRAVO trial, Bayer inappropriately highlights a single secondary efficacy outcome (i.e., all-cause mortality) and disregards the primary efficacy outcome and all the other secondary outcomes, as well as the study's key aspirin safety results.

In addition, Bayer cites an abstract by Aronow et al. (2003)[20] that describes this same all-cause mortality finding from the BRAVO trial and, based on this, asserts that a higher dose of aspirin provides greater efficacy. Bayer's focus on all-cause mortality (i.e., death) fails to acknowledge the principal benefit of cerebro- and cardiovascular (CV) preventive aspirin therapy, which is reduction in risk of myocardial infarction (MI) or of composite endpoints (MI + stroke + CV death), not a reduction in all-cause mortality alone.[21]

As detailed in McNeil's Petition, Topol et al. (2003) reported results from the BRAVO study, a randomized, double-blind, placebo-controlled, study of lotrafiban, an oral GP IIb/IIIa antagonist, in patients with coronary and/or cerebrovascular disease.[19] All subjects received aspirin at a dose ranging from 75–325 mg/day. A total of 9190 patients from 23 countries were enrolled in the study. Safety endpoints included the incidence of serious bleeding, any bleeding, or any transfusion. The incidence of serious bleeding (2.4% vs. 3.3%), any bleeding (11.1% vs.15.4%), or any transfusion (1.0% vs. 2.0%) in the aspirin alone group was lower among subjects receiving 75–162 mg/day aspirin compared to greater than 162 mg/day aspirin, respectively.

The BRAVO study compared the efficacy of low-dose (75–162 mg/day) (n=2410) and higher doses of aspirin (>162 mg/day) (n=2179). Table 3 provides a summary of the incidence of the composite endpoint and individual components of the composite endpoint by daily dose of aspirin.

Table 3. Incidence of the Composite Endpoint and Individual Components of the Composite Endpoint by Aspirin Daily Dose – (Topol et al., 2003)[19]

	Outcomes by Aspirin Daily Dose	
Outcome	**Low Dose (75–162 mg/day) (n=2410)**	**High Dose (>162 mg/day) (n=2179)**
Primary endpoint[a]	16.4%	18.6%
Death, MI, stroke	6.2%	6.1%
Death	2.8%	1.7%
MI	2.0%	2.1%
Stroke	2.1%	2.8%
Urgent hospitalization	9.5%	10.6%
Urgent revascularization	7.3%	10.0%

Abbreviations: MI: myocardial infarction

a. The primary endpoint was a composite of all-case mortality, MI, stroke, recurrent ischemia requiring hospitalization, and urgent revascularization.

[20] Aronow HD, Califf RM, Harrington RA, et al. Higher dose aspirin is associated with reduced mortality and more serious bleeding in patients with recent cerebrovascular or coronary ischemic events: insights from BRAVO trial. American Heart Association Scientific Sessions. Abstract. November 12, 2003.

[21] 21 CFR § 343.80. Professional Aspirin Labeling.

BRAVO study findings demonstrated that high-dose (>162 mg/day) aspirin was associated with an increased incidence (18.6%) of the primary composite endpoint compared with low-dose (75–162 mg/day) aspirin (16.4%). These results reflect the higher incidence of stroke (low dose: 2.1%; high dose: 2.8%), urgent hospitalization (low dose: 9.5%; high dose: 10.6%), and urgent revascularization (low dose: 7.3%; high dose: 10.0%) among patients taking >162 mg/day of aspirin. There was no between-group difference observed in the incidence of MI (low dose: 2.0%; high dose: 2.1%). Although death occurred at a higher incidence in the low-dose (2.8%) compared to the high-dose (1.7%) aspirin group, there were no other reported between-group differences that favored the higher dose aspirin group. Based on these data, aspirin doses of 75–162 mg/day were as effective as aspirin doses >162 mg/day in reducing the incidence of MI, stroke, and recurrent ischemia requiring hospitalization, and urgent revascularization in patients with coronary artery disease (CAD) or cerebrovascular disease.

In sum, the CURE and BRAVO trials were randomized, double-blind, placebo-controlled studies, which demonstrated the reduction in the incidence of bleeding events with lower doses of aspirin as compared to higher doses. Nothing in Bayer's comments negates the relevance and significance of these aspirin safety data. Despite Bayer's contention that these studies are hypothesis generating, such post-hoc analyses are valid approaches to evaluating safety data and appropriate for regulatory safety reviews.[22,23]

B. THE PHENOMENON OF "ASPIRIN RESISTANCE"

In its comments, Bayer raises the issue of "aspirin resistance". Bayer describes "aspirin resistance" as not only an absence or variance of the expected pharmacolologic effects of aspirin on platelets, but also poor clinical outcomes.

1. Bayer's Citations Of "Aspirin Resistance"

Bayer's cites studies that they claim "...indicate an improved response in patients taking higher doses of aspirin. A total of five studies examined a variety of laboratory platelet function testing devices in patients with cerebro- and cardiovascular diseases who were taking preventive aspirin therapy. Three studies (Alberts et al., 2004[24], Syrbe et al., 2001[25], and Helgason et al., 1993[26]) suggested that an increase in aspirin dose may

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[22]Temple RJ. The regulatory evolution of the integrated safety summary. *Drug Information Journal.* 1991;25:485-492.
[23]Temple RJ. Meta-analysis and epidemiologic studies in drug development and postmarketing surveillance". *JAMA.* 1999;281(9):841-844.
[24] Alberts MJ, Bergman D, Molner E, et al. Antiplatelet effect of aspirin in patients with cerebrovascular disease. *Stroke.* 2004;35:175-178.
[25] Sybre G, Redlich H, Weidlich B, et al. Individual dosing of ASA prophylaxis by controlling platelet aggregation. *Clin Appl Thrombosis/Hemostatis.* 2001;7:209-213.

result in an increase in platelet inhibition. Two other studies reported the possible prevalence of aspirin resistance (Chen et al., 2005)[27] and the association of aspirin resistance with platelet polymorphism (Macchi et al., 2003).[28] None of the five laboratory studies assessed cerebro- and cardiovascular clinical outcomes and, as such, they offer no data to support Bayer's claim.

Two additional studies cited by Bayer—Eikelboom et al. (2002)[29] and Gum et al. (2003)[30] —evaluated possible associations between platelet function testing (urinary thromboxane B2 and optical platelet aggregometry, respectively) and risks of cerebro- and cardiovascular events in patients on various aspirin therapy regimens. Since neither study was designed to assess associations between clinical outcomes and aspirin dose, the possibility of a relationship remains unknown.

In a separate Bayer submission on September 9, 2004 to FDA Docket 77N-0094[31], Bayer commented on "aspirin resistance" indicating that the available scientific evidence was "...essentially unreliable". In their submission document, Bayer provided a summary entitled "Aspirin Resistance" (Vol. 2, Section 11.7 of an Integrated Summary of Efficacy), which reviewed epidemiological studies, measurements of "aspirin resistance" and its possible molecular mechanisms. Bayer's conclusion stated that—

> "The current usage of the term "aspirin resistance" implies a linkage between a laboratory test and a clinical outcome that cannot be substantiated through the current studies at this time. The data currently available is either analytical or descriptive in nature and numerous biases are found, thereby making it essentially unreliable. Currently, serum thromboxane, bleeding time, urinary thromboxane metabolites, and platelet aggregation are the most common tool for explaining the pharmacologic effect of aspirin in an individual. Unfortunately, they carry little to no weight in assessing the clinical outcome in a particular patient. As such, a biochemically verifiable mechanism for aspirin variable

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[26] Helgason CM, Tortorice KL, Winkler SR, et al. Aspirin response and failure in cerebral infarction. *Stroke.* 1993;24:345-350.

[27] Chen WH, Lee PY, Ng W, et al. Prevalence, profile, and predictors of aspirin resistance measure by ultegra rapid platelet function assay-asa in patients with coronary artery disease. ACC Annual Scientific Sessions. Abstract. March 6-9, 2005.

[28] Macchi L, Christiaens L, Brabant S, et al. Resistance in vitro to low-dose aspirin is associated with platelet P1a1 (GP IIIa) polymorphism but not with C807T (GP Ia/IIa) and C-5T Kozak (GP Ib alpha) polymorphism. *J Am Coll Cardiol.* 2003;42:1115-1119.

[29] Eikelboom JW, Hirsh J, Weitz JI, et al. Aspirin-resistant thromboxane biosynthesis and risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation.* 2002;105:1650-1655.

[30] Gum PA, Kotke-Marchant K, Welsh PA et al. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. *J Am Coll Cardiol.* 2003;24:345-350.

[31] Bayer's Supplement to Citizen Petition, Vol. 2, Integrated Summary of Efficacy. FDA Docket 77N-0094, September 9, 2004. p.250-251.

response needs to be defined before concerns regarding such a phenomenon are warranted."

2. Medical Experts' Assessments Of "Aspirin Resistance"

Two recent publications in 2005 are from medical expert panels who considered available scientific evidence in assessing the possible implications of the phenomenon of "aspirin resistance". The first publication[32] was a panel composed of experts in cardiology, gastroenterology, hematology, and clinical pharmacology, who provided the following summary points regarding "aspirin resistance:

- there is no universally accepted definition of "aspirin resistance";
- the mechanisms by which aspirin resistance may be taking place are still unclear;
- the utility of currently available tests in identifying aspirin-resistant patients remains to be defined;
- no data exist to guide aspirin therapy on the basis of platelet function test results.

The second publication, from the Working Group on Aspirin Resistance[33], reported the following conclusions:

- the correct treatment, if any, of aspirin "resistance" is unknown;
- no published studies address the clinical effectiveness of altering therapy based on a laboratory finding of aspirin resistance;
- a clinically meaningful definition of aspirin resistance needs to be developed based on data linking aspirin-dependent laboratory tests to clinical outcomes in patients.

In sum, consensus among medical experts is that there is no accepted definition for "aspirin resistance" and that no data exist to guide aspirin therapy on the basis of laboratory test results. Bayer previously indicated that "aspirin resistance" scientific evidence was "essentially unreliable." In their comments to McNeil's Petition, they offer no data to support their claim of a need for higher doses of aspirin in "aspirin resistant" patients in order to achieve an improved clinical outcome.

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[32] Eikelboom J, Feldman M, Mehta S, et al. Report of Roundtable: Aspirin resistance and its implications in clinical practice. *MedScape General Medicine*. 2005;7(3).

[33] Michelson AD, Cattaneo M, Eikelboom JW, et al. Aspirin resistance: position paper of the *working group on aspirin resistance*, Platelet Physiology Subcommittee of the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis. *J Thrombosis & Haemostasis*. 2005;3:1-3.

C. LOW-DOSE (≤150 MG/DAY) ASPIRIN IS APPROPRIATE FOR SECONDARY PREVENTION IN PATIENTS WITH STROKE, WITH DIABETES, THOSE WHO SMOKE, AND WITH ELEVATED BMI OR BODY WEIGHT

Bayer cites evidence in stroke populations, in patients with diabetes, those who smoke and those with an elevated body mass index (BMI) or body weight, that they contend supports higher doses of preventive aspirin therapy for effectiveness.

1. Aspirin Treatment in Selected Stroke Trials

Bayer asserts that, "Contemporary stroke trials have used higher doses (≥650 mg) of aspirin and demonstrated safety and efficacy, thus supporting the acceptance of higher doses in certain secondary prevention populations." Bayer bases its assertion on the findings of two studies: African American Antiplatelet Stroke Prevention Study (AAASPS)[34] and the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Trial.[35]

AAASPS was a randomized, double-blind, investigator-initiated trial of 1809 black men and women who recently had a noncardioembolic ischemic stroke.[34] Subject recruitment began in December 1992. A total of 902 patients received 500 mg/day of ticlopidine and 907 received 650 mg/day of aspirin. The primary outcome was a composite of recurrent stroke, myocardial infarction or vascular death. Secondary outcomes were fatal and non-fatal stroke. The investigators noted that since the study was designed in the early to mid-1990s, they opted for an aspirin dose of 650 mg/day (based on a single reference, which cited clinical trials published from 1977 to 1991).

WASID Trial was a randomized, double-blind clinical trial of 569 subjects who had symptomatic intracranial arterial stenosis.[35] A total of 280 subjects received 1300 mg/day of aspirin and 289 subjects received warfarin (target INR of 2.0-3.0). Subject recruitment began in February 1999. The primary endpoints were ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke. The investigators noted that their choice of aspirin dose (i.e., 1300 mg/day) was based on findings from published laboratory studies of platelet function, none of which evaluated clinical outcomes.

Bayer suggests, "there remains belief that high doses of aspirin are important and valuable to care for these [stroke] populations." However, neither study cited by Bayer was designed to assess the comparative efficacy nor safety of different aspirin doses because only one dose of aspirin was employed in each study. Also, Bayer's suggestion

[34] Gorelick P, Richardson D, Kelly M, et al. Aspirin and ticlopidine for prevention of recurrent stroke in black patients. *JAMA*. 2003;289:2947-2975.
[35] Chimowitz M, Lynn M, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *NEJM*. 2005;352:1305-1316.

of an emerging awareness of the potential benefits of higher doses (i.e., 650 or 1300 mg daily) of aspirin for patients with stroke is entirely inconsistent with FDA's 1998 Final Rule [63 FR § 56802], Professional Aspirin Labeling. In this 1998 Final Rule, FDA lowered the upper limit of aspirin dosing from 1300 mg/day to 325 mg/day for secondary prevention based upon positive findings at lower dosages (e.g., aspirin 50, 75, 300 mg daily) along with the higher incidence of side effects expected at the higher dosage (e.g., aspirin 1300 mg daily).

2. *Aspirin Treatment in Patients with Diabetes*

In its comments, Bayer notes an observational study by Watala et al. (2004)[36] and an analysis of data from a clinical study, entitled the Primary Prevention Project (PPP)[37], as "evidence that, when compared to nondiabetics, diabetics may require higher doses [aspirin] to achieve comparable levels of effectiveness."

Watala et al. (2004) conducted a crossover design observational study in 31 patients with type 2 diabetes mellitus (n=18 were treated with insulin and n=13 were on oral antidiabetic agents) and 48 healthy age-matched volunteers. The study's aim was to evaluate the sensitivity of platelets to aspirin and whether there is an association between this and metabolic control parameters of diabetes. Study subjects were given 150 mg/day of aspirin for one week; no other aspirin doses were studied. The investigators' reported that poor metabolic control might play a role in the reduced sensitivity to aspirin observed in their diabetic study subjects. The study did not assess cerebro- and cardiovascular clinical outcomes. The investigators acknowledged that, at present, there are no medical data indicating that higher doses of aspirin are more effective in people with diabetes than in nondiabetics.

The Primary Prevention Project (PPP) was a randomized, open-label trial with a two by two factorial design in patients with one or more cardiovascular risk factors, but not a history of an event.[37] Its objective was to explore the effects of 100 mg/day aspirin, 300 mg/day vitamin E, or placebo on the primary composite endpoint of cardiovascular death, stroke, or myocardial infarction. A parallel trial was conducted in 1031 patients with type 2 diabetes to specifically explore the effects of aspirin and vitamin E on the same composite endpoints. Although findings in diabetics showed a nonsignificnat 10% risk reduction in total cardiovascular events, the study was not designed to explore the effects of different aspirin dose regimens on clinical outcomes.

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[36] Watala C, Golanski J, Pluta J, et al. Reduced sensitivity of platelets from type 2 diabetic patients to acetylsalicylic acid (aspirin) – its relationship to metabolic control. *Thrombosis Research*. 2004;113:101-113.
[37] Sacco, M, et al. Primary Prevention of cardiovascular events with low-dose aspirin and vitamin E in type 2 diabetic patients. *Diabetes Care*. 2003;26:3264-3272.

In sum, there are no data in the two studies cited by Bayer to support a claim that patients with diabetes may require higher doses of aspirin for secondary prevention. Also, Bayer's suggestion is inconsistent with the American Diabetes Association's recommendation[38] of using low dose (75–162 mg/day) aspirin therapy as a secondary prevention strategy in diabetic men and women with a history of previous cerebro- or cardiovascular events.

3. Aspirin Treatment In Individuals Who Smoke

Bayer cites two studies that examined the acute effects of smoking on platelet function in a laboratory setting[39,40] and they contend that this evidence supports a conclusion that "higher doses of aspirin may be needed" in smokers.

In the first study by Hung et al. (1995), the subjects were 12 habitual smokers (15–60 cigarettes per day) with a history of stable coronary artery disease, a history of taking 325 mg/day of aspirin and, in 3-4 subjects, of taking other concomitant cardiovascular medications.[40] Each subject had his or her blood drawn before and immediately after smoking two cigarettes. Platelet function was tested in a porcine model simulating a deep arterial injury, which exposes a highly thrombogenic arterial media surface. Platelet aggregometry and plasma coagulation parameters were also evaluated. Using this porcine aorta model, the authors reported a non-significant increase in platelet thrombus (5 of 12 subjects had no increase or a decrease in platelet thrombus) at the low shear rate after smoking and a significant increase in thrombus formation (3 of 12 subjects had a decrease in platelet thrombus) at the high shear rate after smoking. Platelet aggregometry results were reported as significant, but plasma coagulation values were not significant.

The second study, by Kalliakmanis et al. (2000), evaluated platelet aggregation in 54 habitual smokers (2 to 60 cigarettes per day) without a history of cerebro- or cardiovascular disease.[39] Subjects had their blood drawn before and immediately after smoking one cigarette. Platelet function was measured using turbidometric platelet aggregometry. The authors reported a significant relationship between the observed rates of platelet aggregation before and after smoking one cigarette. Other analyses suggested "the number of cigarettes smoked per day."

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[38] American Diabetes Association. Aspirin therapy in diabetes. *Diabetes Care*. 2004;27(1):S72-73

[39] Kalliakmanis A, Harisi M, Manolis E, et al. The acute effect of smoking a cigarette in ex vivo ADP platelet aggregation in habitual smokers. *Haema*. 2000;3(4):229-232.

[40] Hung J, Lam J, Lacosta L, et al. Cigarette smoking acutely increases platelet thrombus formation in patients with coronary artery disease taking aspirin. *Circulation*. 1995;92:2432-2436.

The significant limitations with these studies render Bayer's claim unsupportable:

- the studies employed experimental ex-vivo models and/or laboratory tests whose predictive value and relevance to actual cerebro- and cardiovascular outcomes is unknown;
- the studies' lack nonsmoker control groups, which result in an inability to assess the relationship between smoking status and platelet activity;
- the lack of a comparative aspirin dose group in the study by Hung et al. (1995) does not allow an assessment of the relationship between aspirin dose and platelet activity;
- the study by Kalliakmanis et al. (2000) did not include any aspirin group; therefore, there is no support for a potential relationship between the effect of smoking on preventive aspirin therapy;
- the study population in the study by Kalliakmanis et al. (2000) comprised healthy volunteers and, therefore, is not the target population for secondary preventive aspirin therapy.

4. Aspirin Treatment in individuals With Elevated BMI and Body Weight

Bayer cites three studies as support for their claim that "patients with elevated BMI and body weight may require higher doses of aspirin for effectiveness."

The first study is an abstract by Cox et al. (2004)[41] that reported three studies of 75 total subjects who received at least two and up to five forms of aspirin. Serum thromboxane B_2 was measured before and after 14 days of aspirin (75 mg/day) treatment. Based on a secondary study finding, the investigators noted a significant correlation between body weight and percent inhibition of serum thromboxane B_2 following aspirin treatment. Such a study conclusion is unsubstantiated for the following reasons:

- this study employed laboratory tests whose predictive value and relevance (if any) to cerebro- and cardiovascular clinical outcomes is unknown;
- this study was not designed to evaluate a potential correlation between BMI or body weight and aspirin dose, because only one dose strength of aspirin was studied;
- subjects were not stratified a priori by body mass index or body weight.

The second study, by Tamminen et al. (2003) enrolled 21 nondiabetic subjects and assigned them to two groups (i.e., "obese" and "nonobese") based on median body

[41] Cox D, Maree A, Dooley M, et al. Lower bioavailability and weight dependence of enteric-coated aspirin preparations. Fifth Annual Conference on Arteriosclerosis, Thrombosis, and Vascular Biology. Abstract. May, 2004.

mass index.[42] Subjects were given aspirin 50 mg one time. The study objective was to determine whether obesity-associated insulin resistance was characterized by altered aspirin sensitivity of platelet aggregation. The investigators reported that aspirin inhibition of platelet aggregation was "blunted" in obese insulin resistant subjects compared to the nonobese group. Such a study conclusion is unsubstantiated for the following reasons:

- this study employed laboratory tests whose predictive value and relevance (if any) to cerebro- and cardiovascular clinical outcomes is unknown;
- the study was not designed to evaluate a potential correlation between BMI or body weight and aspirin dose, because only one dose strength of aspirin was studied.

Bayer cites The Women's Health Study[43], a two-by-two factorial trial evaluating the balance of risks and benefits of low-dose aspirin (100 mg every other day was the only dose used) and vitamin E (600 IU every other day) in the primary prevention of cardiovascular disease and cancer.

Bayer misinterprets data from The Women's Health Study pertaining to BMI and risk of major cardiovascular events when they state, "Subgroup data stratified by baseline BMI (<25, 25–29, >30) reflects potential differences in response to aspirin. Women in the lowest BMI subgroup demonstrated a beneficial response in terms of cardiovascular event reduction compared to those in the highest subgroup." In fact, within the lowest BMI subgroup, there were fewer major cardiovascular events in the aspirin group compared to that of the placebo group; this finding was a statistically significantly difference (p=0.05). Within the highest BMI subgroup, there was no significant difference in the number of major cardiovascular events (p=0.72). However, these within-subgroup results did not indicate a difference in aspirin's effects across the two BMI subgroups, as Bayer contends.

As noted in the statistical analysis section, the investigators in the Women's Health Study assessed modification of the effect of aspirin by the risk factors studied using interaction terms between subgroup indicators and aspirin assignment, with tests for trend performed when subgroup categories were ordinal. Based on this assessment, it is clearly stated among the study results for subgroup analyses, which included body-mass index, that, "there was no evidence that any of the cardiovascular risk factors considered, except smoking status and age, modified the effect of aspirin on the primary

[42] Tammienen M, Lassial R, Westerbacka J, et al. Obesity is associated with impaired platelet-inhibitory effect of acetylsalicylic acid in nondiabetic subjects. *International Journal of Obesity*. 2003;27:907-911.
[43] Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *NEJM*. 2005;352:1293-1304.

endpoint of major cardiovascular events." Therefore, there was no evidence that BMI had a statistically significant effect on aspirin and major cardiovascular effects.

In conclusion, no data in the three studies cited by Bayer support their claim that "patients with elevated BMI and body weight may require higher doses of aspirin for effectiveness."

D. PROFESSIONAL HEALTHCARE ORGANIZATION SUPPORT FOR LOW-DOSE ASPIRIN FOR SECONDARY PREVENTION

Bayer cites the 2001 American Heart Association (AHA) / American College of Cardiology (ACG) Guidelines for Preventing Heart Attack and Death in Patients with Atherosclerotic Cardiovascular Disease and refers to this guideline as support for higher doses (i.e., up to 325 mg daily) of aspirin for secondary prevention.

More current guidelines from professional healthcare organizations published in 2004 recommend preventive aspirin therapy doses that are consistent with McNeil's Petition request:

- 2004 ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction recommend a daily dose of aspirin 75 to 162 mg to be continued indefinitely in patients recovering from myocardial infarction.[44]
- Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy: Evidence-Based Guidelines specifies the use of the lowest effective dose of aspirin (i.e., 50–100 mg daily for long-tern treatment) for preventive therapy of cerebro- and cardiovascular events.[45]
- The American Diabetes Association recommends the use of aspirin therapy (75–162 mg/day) as a secondary prevention strategy in diabetic men and women with a history of myocardial infarction, vascular bypass procedure, stroke or transient ischemic attack, peripheral vascular disease, claudication, and/or angina.[38]

In addition, both the American College of Gastroenterology (ACG) and the National Stroke Association (NSA) have submitted comments to FDA Docket 2005P-0048 urging FDA to approve McNeil's Citizen Petition, and to amend the professional labeling for aspirin to change/reduce the maximum daily dose to 150 mg/day for both secondary

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[44] Antman EM, Anbe DT, Armstrong PW, et al. *ACC/AHA Practice Guidelines.* ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Developed in Collaboration With the Canadian Cardiovascular Society. ACC Foundation and the AHA, Inc. 2004; e1-e212.

[45] Patrono C, Collier B, Fitzgerald GA, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects. The seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest.* 2004;126:234S-264S.

cardiovascular prevention, and to 150 mg/day for secondary cerebrovascular prevention.[46, 47]

I. CONCLUSIONS

McNeil's Petition is supportive of FDA's Risk Minimization initiatives which focus on the appropriate drug at the appropriate dose in order to minimize the risk to patients while ensuring beneficial effects. As it relates to aspirin therapy for secondary cardio- and cerebrovascular prevention, McNeil's Petition provides a comprehensive evidence-based risk assessment in relation to the benefits of low-dose (≤150 mg daily) aspirin. Since aspirin daily doses >150 mg do not provide superior efficacy when compared with aspirin daily doses of ≤150 mg, recommending higher (>150 mg daily) aspirin doses merely exposes patients to a higher risk of major bleeding events, particularly GI bleeding.

Overall, nothing in Bayer's comments negates the significance of the scientific evidence supporting McNeil's Petition. Moreover, Bayer's comments direct attention away from the important public health need, as well as the scientific evidence supporting the need for professional aspirin labeling that provides a more favorable benefit/risk profile with low-dose (≤150 mg/day) aspirin therapy for secondary cardio- and cerebrovascular prevention:

- Clinical Trials Supporting Low Dose (≤150 mg/day) Aspirin Safety and Efficacy
  Nothing in Bayer's comments negates the significance of the body of clinical trial data provided in McNeil's Petition. Evidence from randomized clinical trials demonstrates a reduction in the risk of major bleeding events with low-dose (≤150 mg/day) aspirin as compared to high-dose (>150 mg/day) aspirin; low-dose (≤150 mg daily) aspirin has been demonstrated to be as effective as high-dose (>150 mg) aspirin for the prevention of serious vascular events (nonfatal myocardial infarction, nonfatal stroke, or vascular death).

- The Phenomenon of "Aspirin Resistance"
  Consensus of medical experts is that there is no accepted definition for "aspirin resistance" and that no data exist to guide aspirin therapy on the basis of laboratory test results. Bayer offers no data to support the claim of a need for higher doses of aspirin in "aspirin resistant" patients in order to achieve an improved clinical outcome.

[46] American College of Gastroenterology. Letter to the FDA Docket 2005P-0048, May 4, 2005.
[47] National Stroke Association. Letter to FDA Docket 2005P-0048. May 23, 2005.

- Patient Subpopulations
  Bayer presents no data to support its claim that patients with stroke, with diabetes, those who smoke, and those with an elevated BMI or body weight may require higher doses of aspirin for effectiveness. Low-dose (≤150 mg daily) aspirin therapy is appropriate for secondary cardio- and cerebrovascular prevention in such subpopulations.

- Healthcare Professional Organization Guidelines
  In contrast to Bayer's contention, current guidelines from professional healthcare organizations published in 2004 recommend preventive aspirin therapy doses that are consistent with McNeil's Petition request.

For these reasons, McNeil renews its request for FDA action to approve a change in the professional aspirin labeling for aspirin dosing under 21 C.F.R. § 343.80, in order to specify the more favorable benefit/risk profile of aspirin doses of 75–150 mg/day for secondary cardiovascular prevention, and aspirin doses of 50–150 mg/day for secondary cerebrovascular prevention.

Respectfully yours,
MCNEIL CONSUMER & SPECIALTY PHARMACEUTICALS

Minnie Baylor-Henry, JD
Vice-President, Medical and Regulatory Affairs

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